REMARKS

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections under 35 USC § 103

Claims 26-29, 32-34, and 63-68 remain rejected as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/01, 2(15): 1-9) in view of Flanagan et al. (WO 96/26958; 9/6/96) and Genentech (WO 00/30673; 6/2/00), for the reasons stated in the Office Action of 10/7/08, for the reasons stated in the Office Action of 3/9/09, and for the reasons set forth in the Office Action of 6/7/10.

The Office admits that in the Reply of 3/19/10, Applicants correctly state that:

1) the antibodies of Stephenson et al. do not promote apoptosis,

2) the antibodies of Flanagan et al. do not bind EphB4 and do not promote apoptosis,

3) the antibodies of Genentech do not bind EphB4 and do not promote apoptosis, and

4) that siRNA mediated knock-down of EphB4 protein production, which results in apoptosis, is not biologically equivalent to an antibody binding to the extracellular domain of EphB4.

However, the Examiner maintains the rejection based on the combination of Stephenson et al., Flanagan et al., and Genentech, even though the only actual EphB4 binding antibody taught by the references unequivocally does not promote apoptosis. To arrive at this rejection, the Office relies on a finding of inherency as evidenced by Xi et al. (Clinical Cancer Research, June 2005, 11(12): 4305-4315). Xi et al. shows that siRNA-mediated ablation of EphB4 triggers apoptosis in mesothelioma cells. But Xi et al. does not show that an antibody that binds to EphB4 must necessarily promote apoptosis because the results of Xi et al. are amenable to multiple explanations, most of which are not consistent with an EphB4-binding antibody being capable of inducing

apoptosis. Indeed, on page 4313, Xi et al. admit that apoptosis resulting from EphB4 knock-down may be the result of a ligand-independent mechanism. A similar understanding is expressed in Kumar et al. (American Journal of Pathology, July 2006, 169(1): 279-293) where results similar to those of Xi et al. are reported – namely, that siRNA-mediated ablation of EphB4 triggers apoptosis in breast cancer cells. As in Xi et al., on page 292, Kumar et al. admit that their results are consistent with multiple theories of EphB4 function. For example, "[s]uch events may result from self-aggregation and receptor activation due to high receptor density. . . . Alternatively, EphB4 may function in a signaling-independent mechanism, wherein interaction of EphB4 with certain components of death receptor pathway can interrupt apoptotic signals." Furthermore, Xi et al. provide additional uncertainty to the interpretation of the results because Xi et al. report that siRNA-mediated ablation of Ephrin B2 does not cause apoptosis in mesothelioma cells. This result suggests that inhibition of Ephrin B2/EphB4 signaling would not induce apoptosis and further suggests that some alternative ligand-independent or signaling-independent mechanism is the underlying cause of the apoptosis resulting from the knock-down of EphB4. As the Office admits, siRNA mediated knock-down of EphB4 is not biologically equivalent to an antibody binding the extracellular domain of EphB4. Therefore, even though siRNA knock-down triggers apoptosis, there is no support for the notion that EphB4-binding antibodies could disrupt the ligand-independent or signaling-independent EphB4 functions mentioned in Xi et al. and Kumar et al. Given the uncertainty in the interpretation of the results of Xi et al. and Kumar et al., there is no motivation to produce an EphB4-binding antibody that promotes apoptosis, and there certainly would be no reasonable expectation of success. Furthermore, this is not a situation where the prior art provided a finite number of identified, predictable solutions that would lead a person of skill to derive the claimed antibody. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency.]" *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981). "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966). "Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

Finally, even if the Office did make a *prima facie* showing of obviousness, and it did not, the June 6, 2010 Office Action did not address the fact that Queen Elizabeth Hospital (WO 2004/024773) and Stephenson et al. teach away from EphB4 antibodies that promote apoptosis because the H-200 antibody of Stephenson et al. – the only EphB4-binding antibody described in the cited prior art – unequivocally does ***not*** induce apoptosis.

CONCLUSION

In view of the above remarks, Applicants believe that the pending application is in condition for allowance. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (617) 951-7000. Applicants believe that no fee is due. However, if an additional fee is due, please charge our Deposit Account No. **18-1945**, under Order No. **VASG-P01-002** from which the undersigned is authorized to draw.

Dated: July 2, 2010

Respectfully submitted,

By__/Andrew W. Shyjan/__
Andrew W. Shyjan, Ph.D., J.D.
Registration No.: 61,294
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant